

Appl. No.            :       09/816,763  
Filed                :       March 23, 2001

## REMARKS

The following addresses the substance of the Office Action.

### Priority

The Examiner asserts that Applicant cannot rely upon its foreign priority because a translation of the foreign priority document has not been received. It is Applicants understanding that the priority document is in English. Applicants thank the Examiner for the teleconference with Applicants representatives on July 6, 2005 in which the Examiner agreed to review the priority document and to contact Applicants representatives prior to preparing any subsequent action in this application if the priority document is not in English.

### Claim objections

Claims 1, 2, 4-8, 12-15, 17, 18, 22, 34, 36 and 37 have been objected to for being grammatically unclear for reciting the phrase “a non-radioactive resulting signal”. Claim 4, which is the only claim reciting the objected phrase has now been amended to recite “a non-radioactive signal”. Therefore, Claims 1, 2, 4-8, 12-15, 17, 18, 22, 34, 36 and 37 are now clear.

Claims 1, 2, 4-8, 12-18, 22, 34, 36 and 37 have been objected to for containing a period after each sub-step. Claims 1 and 16 which contain the periods after each substep have been amended accordingly.

Claims 19-21 have been objected to being drawn to a separate invention, which can not be practiced together with the elected invention. Claims 19-21 have been amended to further clarify their relationship to the invention of Claim 1.

### Compliance with 35 USC §112

The Examiner has rejected Claims 1, 2, 4-8, 12-18, 22, 34, 36 and 37 under 35 USC §112, second paragraph as being indefinite. More specifically, Claims 1 and 16 were found indefinite for reciting the phrase “said double-stranded DNA sequence being connected to the surface of the solid support by a spacer *corresponding to* or comprising at least a double-stranded DNA nucleotide sequence” as it is unclear what the difference is inferred between “corresponding to” and “comprising”. The independent Claims 1 and 16 have been amended to now recite “wherein said spacer is a double-stranded DNA nucleotide sequence of between about 50 and about 250 base pairs, or wherein the spacer comprises a double-stranded DNA nucleotide

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sequence of between about 50 and about 250 base pairs". Therefore, Claims 1, 2, 4-8, 12-18, 22, 34, 36 and 37 are now definite.

Claim 14 was found indefinite for having insufficient antecedent basis for the phrases "the specific sequence" and "the same molecule". Claim 14 has been amended to now recite "wherein the double-stranded DNA sequence comprises repeated specific sequences". Therefore, Claim 14 is now definite.

Claim 22 was found indefinite for having insufficient antecedent basis for the phrase "the consensus sequence". Claim 22 has now been amended to recite "the specific sequence". Therefore Claim 22 is now definite.

Applicant has addressed all the rejections under 35 USC §112, second paragraph of Claims 1, 2, 4-8, 12-18, 22, 34, 36, and 37, which are now definite. Therefore, their rejection should be withdrawn.

#### **Compliance with 35 USC §103**

The Examiner has rejected Claims 1, 2, 4-8, 12-18, 22, 36 and 37 under 35 USC §103(a) as being allegedly unpatentable over Peterson et al (USP 5,563,036) in view of Heslot et al. (USP 6,342,353 having a 102(e) date of November 4, 1999) and Nerenberg et al. (US 2002/0015198 with priority date of September 20, 2000). More specifically, the Examiner has stated that it would have been obvious to a person with an ordinary skill in the art at the time the invention was made to modify the teachings of Peterson et al. with that of Heslot et al. and Nerenberg et al. to arrive at the claimed invention.

The rule is that to establish a *prima facie* case of obviousness, the PTO must cite one or more references that provide some suggestion or motivation to modify the references to achieve the claimed invention, provide a reasonable expectation of success to achieve the claimed invention, and finally, the cited art must teach or suggest all the claim limitations. *In re Vaack*, 947 F.2d 488 (Fed. Cir. 1991).

Furthermore, "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

Here, the cited art either taken alone or in combination, fails to provide the required factors.

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As correctly observed by the Examiner, Peterson et al. neither suggest nor mention the use of a spacer between about 50 and about 250 bp as recited in the independent Claim 1. As was described in the Inventor's Declaration submitted previously (October 2, 2004), use of spacers between about 50 and about 250 bp in length provides enhanced signal levels relative to the levels observed when the binding site is separated from the support by shorter sequences with a length similar to those described in Peterson. These enhanced signal levels are particularly important in the context of microarrays, in which the binding of multiple factors to their recognition sites is evaluated under uniform binding conditions which may be suboptimal for the binding of at least some of the factors. In such situations, it is desirable to enhance signal levels as much as possible since the suboptimal binding conditions may result in a lower degree of binding than would be observed under optimal conditions. In this regard, it is important to note that the methods of Peterson are performed on multiwell plates as opposed to the microarrays utilized in the present methods. Thus, use of 10 bp sequences before the binding site as disclosed in Peterson is insufficient for use in the context of microarrays.

As was stated in the Inventor's Declaration under 37 C.F.R. §1.132 submitted previously, spacers between about 50 bp and about 250 bp provide advantages in binding efficiency. As described in the Declaration, the inventors first performed quantitation of signals resulting from NF-kB binding to recognition sites linked to spacers of various sizes: from 6 bp (close to conditions used by Peterson et al., where the spacer was 8 bp long) to 100 bp. Signal strengths for NF-kB binding were maximum with a spacer of 100 bp.

As was described in the Declaration, similar experiments revealed that increasing spacer lengths increased signal intensities for 4 transcription factors, Elk-1, c-Myk, STAT1 and STAT3, in addition to NF-kB. In addition, as was described in the Declaration, it was possible to detect and quantify 5 different transcriptional factors with accuracy on a microarray under the same binding conditions. Furthermore, contrary to detection of NF-kB factor which was still detectable with the use of a small spacer (6 bp), some factors were hardly detectable (STAT3), or not detected at all (Elk-1) with a small spacer. The inventors also found that the signals measured with spacers below about 50 bp may not increase linearly with the spacer size. Therefore, high variability in signal detection using short (6 bp) spacers is totally incompatible with the simultaneous analysis of more than one factor as claimed in the present invention. Because the

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binding conditions would be uniform on the array, it is likely that the binding conditions (salt concentrations, temperature, etc.) would be less than optimal for each of transcription factors. In view of the suboptimal binding conditions, the optimal spacer size provides important advantages in detecting and quantifying transcription factor binding. The inventors showed in the Declaration that the signals for all the tested transcription factors when tested simultaneously on a single array were maximal when the spacers were between about 50 and 150 basepairs. Therefore, the spacers between about 50 and about 250 base pairs are not obvious in view of Peterson et al.

Heslot et al. (US Patent 6 342 353B1) describes the use of a spacer arm which could be a double-stranded DNA having a length between 100 and 500 bases. However, this US patent is related to a non-analogous field of technology which concerns identification of signatures corresponding to specific sequences of double-stranded nucleic acids by separating the two strands of a nucleic acid duplex each attached to a separate support by a spacer, and then measuring the force necessary to move apart the two supports.

Furthermore, the third paragraph of column 4 (lines 16 to 17) referred by the Examiner, states that nucleotide sequences linked to a slide via the molecular construct (spacer arm) have some freedom of movement but that the length of the spacer arm may be advantageously adjusted in relation to the spatial resolution of the system for locating the position of the beads. Heslot et al. does not teach or suggest to the person skilled in the art that this "freedom of movement" of double-stranded DNA nucleotide sequence used to improve the measurement of the separation forces needed to move apart the two strands of a DNA pair, will also improve the binding of transcriptional factors upon a specific sequence of the double-stranded DNA, in specific conditions, wherein the solid support is a micro-array. In particular, the previous Declaration by the inventor shows that a spacer of a specific length will allow firstly the improvement of detection of some specific transcriptional factors (some transcriptional factors were detected by the use of small spacers, while other transcriptional factors are not detected) and would also improve the high variability in signal detection observed upon micro-array. Such unexpected results are not resulting from a "possible freedom of movements" of the bound double-stranded DNA sequences, but from the binding characteristics of the transcriptional factors to these DNA sequences. Indeed, the specific length of the spacer is important for improving the detection due

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to the possible interference obtained with the solid support surface which reduces the possible binding characteristics of these transcriptional factors to their corresponding sequences.

Nerenberg et al. (with priority date of September 20, 2000) is not prior art over the present application, which is entitled to the priority date of March 24, 2000. The Applicant will submit the certified translation of the priority document shortly to support such entitlement.

In conclusion, Peterson et al. and Heslot et al. failed to support *prima facie* case of obviousness. These references both fail because neither provides the requisite motivation to combine, the reasonable expectation of success, or teaches all the limitations of the claimed invention. Because of these deficiencies, Applicants submit that the PTO failed to articulate a *prima facie* case of obviousness, and as such, request that the present rejection of Claims 1, 2, 4-8, 12-18, 22, 36 and 37 should be withdrawn.

The Examiner has rejected Claim 34 under 35 USC §103(a) as being allegedly unpatentable over Peterson et al (USP 5,563,036) in view of Heslot et al. (USP 6,342,353 having a 102(e) date of November 4, 1999) and Nerenberg et al. (US 2002/0015198 with priority date of September 20, 2000) and further in view of Dattagupta et al. (USP 4,968,602). More specifically, the Examiner stated that it would have been obvious to a person with an ordinary skill in the art at the time the invention was made to modify the teachings of Peterson et al. with that of Heslot et al. and Nerenberg et al. to substitute the avidin with streptavidin of Dattagupta et al. to arrive at the claimed method involving streptavidin/biotin binding.

The non-obviousness of Claims 1 and 12, to which Claim 34 depends, over Peterson et al. and Heslot et al. and irrelevance of Nerenberg et al. is discussed above. Dattagupta et al. fails to cure the deficiencies of the primary references. Therefore, Claim 34 is non-obvious over the cited references and its rejection under 35 USC §103(a) should be withdrawn.

### **Double Patenting**

The Patent Office rejected claims 1, 2, 4-8, 12-18, 22, 34, 36 and 37 on the grounds of obviousness-type double patenting over claims 1-21, 25 and 26 of copending Application No. 10/821,568. A terminal disclaimer may be used to overcome an obviousness-type double patenting rejection. Applicant will defer filing a terminal disclaimer until the rejected claims are otherwise indicated to be in condition for allowance.

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### CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action are inapplicable to the present claims. Accordingly, Applicants request the expeditious allowance of the pending claims.


The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is respectfully requested to call the undersigned at the below-given phone number, to discuss such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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